ClinicalEvidence

Jet lag

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ABSTRACT

INTRODUCTION: Jet lag is a syndrome caused by disruption of the 'body clock', and affects most air travellers crossing five or more time zones; it is worse on eastward than on westward flights. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions to prevent or minimise jet lag? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found five studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: hypnotics, lifestyle and environmental adaptations, and melatonin.

QUESTIONS

INTERVENTIONS

Footnote

*The adverse effects of melatonin have not yet been adequately investigated.

Key points

- Jet lag is a syndrome associated with long-haul flights across several time zones, characterised by sleep disturbances, daytime fatigue, reduced performance, gastrointestinal problems, and generalised malaise.

  It is caused by a disruption of the 'body clock', which gradually adapts under the influence of light and dark, mediated by melatonin secreted by the pineal gland: darkness switches on melatonin secretion; exposure to strong light switches it off.

  The incidence and severity of jet lag increase with the number of time zones crossed; it is worse on eastward than on westward flights.

- Melatonin reduces subjective ratings of jet lag on eastward and on westward flights compared with placebo.

  The adverse effects of melatonin have not been systematically studied, but people with epilepsy and people taking an oral anticoagulant should not use it without medical supervision.

  There may be a risk of fixed drug eruption, an allergic manifestation, with melatonin.

  Routine pharmaceutical quality control of melatonin products is necessary.

- Hypnotics (zopiclone or zolpidem), taken before bedtime on the first few nights after flying, may reduce the effects of jet lag by improving sleep quality and duration but not other components of jet lag.

  Hypnotics are associated with various adverse effects, including headache, dizziness, nausea, confusion, and amnesia, which can outweigh any short-term benefits.

- We found no studies that examined the effectiveness of lifestyle or environmental adaptations (such as eating, avoiding alcohol or caffeine, sleeping, daylight exposure, or arousal).

  After a westward flight, it is worth staying awake while it is daylight at the destination and trying to sleep when it gets dark. After an eastward flight, one should stay awake but avoid bright light in the morning, and be outdoors as much as possible in the afternoon. This will help to adjust the body clock and turn on the body's own melatonin secretion at the right time.

DEFINITION

Jet lag is a syndrome associated with long-haul flights across several time zones, characterised by sleep disturbances, daytime fatigue, reduced performance, gastrointestinal problems, and generalised malaise. [1] As with most syndromes, not all of the components must be present in any one case. It is caused by the 'body clock' continuing to function in the day–night rhythm of the place of departure. The rhythm adapts gradually under the influence of light and dark, mediated

by melatonin secreted by the pineal gland: darkness switches on melatonin secretion; exposure to strong light switches it off.

INCIDENCE/ PREVALENCE Jet lag affects most air travellers crossing five or more time zones. The incidence and severity of jet lag increase with the number of time zones crossed.

AETIOLOGY/ RISK FACTORS Someone who has previously experienced jet lag is liable to do so again. Jet lag worsens with the more time zones crossed in one flight, or series of flights, within a few days. Westward travel causes less disruption than eastward travel as it is easier to lengthen, rather than to shorten, the natural circadian cycle. [2]

PROGNOSIS Jet lag is worst immediately after travel and gradually resolves over 4 to 6 days as the person adjusts to the new local time. [2] The more time zones crossed, the longer it takes to wear off.

AIMS OF INTERVENTION To prevent or minimise jet lag, with minimal adverse effects.

OUTCOMES **Severity of jet lag**, including subjective jet lag score and daytime alertness; **Sleep quality and duration**; **Adverse effects** of treatment.

METHODS *Clinical Evidence* search and appraisal January 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2014, Embase 1980 to January 2014, and The Cochrane Database of Systematic Reviews 2013, issue 12 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published systematic reviews and RCTs, at least single-blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 16). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions to prevent or minimise jet lag?

OPTION MELATONIN

- For GRADE evaluation of interventions for Jet lag, see table, p 16 .
- Melatonin reduces subjective ratings of jet lag on eastward and on westward flights, compared with placebo.
- Melatonin has been associated with possible adverse effects, and its pharmacology and toxicology are unclear. People with epilepsy or taking warfarin (or another oral anticoagulant) should not use melatonin without medical supervision.
- There may be a risk of fixed drug eruption, an allergic manifestation, with melatonin.
- Routine pharmaceutical quality control of melatonin products is necessary.

Benefits and harms

Melatonin versus placebo:

We found one systematic review (search date 2008, 10 RCTs, 975 people) comparing melatonin versus placebo. [2] Nine of the included RCTs were in civilian air travellers. In the RCTs, melatonin was given in a varying combination of: before the flight, on the day of the flight, and after the flight. Four RCTs reported global jet lag scores that could be combined. The review found one RCT that examined the effects of melatonin after arrival, and before and after arrival, versus placebo. However, this small RCT (52 people) was in international airline cabin crew completing a nine-day tour of duty, and the results may not be generalisable to the general population. We have therefore reported this trial in the comment section (see Comment).

Severity of jet lag

Melatonin compared with placebo Melatonin may be more effective than placebo at reducing jet lag scores after eastward and westward flights (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Jet lag score					
[2] Systematic review	142 travellers on eastward flights 4 RCTs in this analysis	**Weighted mean subjective jet lag score** 30.9 with melatonin 50.7 with placebo Subjective jet lag score (single scale 0–100 where 0 = no jet lag and 100 = extreme jet lag)	WMD –19.52 95% CI –28.13 to –10.92	○○○	melatonin
[2] Systematic review	90 travellers on westward flights 2 RCTs in this analysis	**Weighted mean subjective jet lag score** 22.3 with melatonin 40.6 with placebo Subjective jet lag score (single scale 0–100 where 0 = no jet lag and 100 = extreme jet lag)	WMD –17.27 95% CI –27.28 to –7.26	○○○	melatonin
[2] Systematic review	47 travellers on eastward flights 2 RCTs in this analysis	**Subjective jet lag score >60** 4/23 (17%) with melatonin 16/24 (67%) with placebo Subjective jet lag score (single scale 0–100 where 0 = no jet lag and 100 = extreme jet lag)	RD –0.50 95% CI –0.74 to –0.25	○○○	melatonin

Sleep quality

Melatonin compared with placebo Melatonin may be more effective than placebo at improving sleep quality in people on eastward flights (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[2] Systematic review	234 travellers on eastward flights Data from 1 RCT	**Sleep quality** with melatonin with placebo Absolute results not reported	P <0.05	○○○	melatonin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[2] Systematic review	Travellers on eastward and westward flights 9 RCTs in this analysis	**Adverse effects** with melatonin with placebo Absolute results not reported The review noted that most RCTs did not look for adverse effects systematically, and many symptoms were difficult to distinguish from symptoms or manifestations of jet lag itself For full details see Further information on studies	The adverse effects of melatonin have not yet been adequately investigated See Further information on studies		

Melatonin plus zolpidem:
See option on Hypnotics, p 5 .

Further information on studies

[2] The review reported that melatonin reduced the symptoms of jet lag in eight RCTs, whereas two RCTs found no effect on symptoms between melatonin and placebo (see Comment section).

[2] The adverse effects of melatonin have not yet been adequately investigated. One RCT found no significant difference between melatonin and placebo in adverse effects; another found that a disorientating 'rocking' feeling was significantly more frequent with melatonin (P = 0.036). Hypnotic effects after melatonin occurred in five RCTs included in the review, [2] affecting about 10% of people (further details not reported). Other effects included headache or heavy head (2 RCTs); disorientation (1 RCT); ear, nose, and throat problems; nausea; and gastrointestinal problems (absolute numbers not reported; P values not reported). One person had difficulty in swallowing and breathing within 20 minutes of taking melatonin. Symptoms subsided after 45 minutes. They recurred after a further dose of melatonin. The review reported that the adverse events in the trials occurred during treatment and seemed to have been short-lived. The review noted that the pharmacology and toxicology of melatonin had not been systematically studied. It found six published and 19 unpublished case reports of possible related adverse effects on the central nervous system (including confusion, ataxia, headache, and convulsant effects), blood clotting (prothrombin increased or decreased, suspected interaction with warfarin), cardiovascular system (including chest pain and dyspnoea), and skin (fixed drug eruption). Although it noted the difficulty of interpreting such data, it questioned the safety of melatonin in people with epilepsy and in people taking warfarin or other oral anticoagulants. It suggested that people in these groups should not use melatonin without an informed (medical) discussion, and concluded that further investigation was needed. It also noted the reports of fixed drug eruption, an allergic manifestation, appear to be convincing and must be taken seriously.

Comment:

Melatonin after arrival, and before and after arrival, versus placebo
One RCT compared melatonin after arrival, and melatonin before and after arrival, with placebo in 52 international airline cabin crew members completing a nine-day tour of duty. Melatonin after arrival reduced the severity of jet lag (P <0.005; absolute results not reported) and improved sleep quality (P <0.01; absolute results not reported) compared with placebo. The RCT reported that reduction in the severity of jet lag was no better with melatonin taken before and after arrival than with placebo but significance was not assessed. The review noted that it is difficult to generalise from the findings of this RCT because the airline staff had complex disordered circadian rhythms due to rapidly repeated flights.

General comments
The trials included in the review [2] did not state whether travellers were frequent flyers or not. Two RCTs found no effect on symptoms with melatonin. [2] In the first of these RCTs, the review

noted that there was probably insufficient time between inward and outward flights for participants to have fully adjusted to the new time zone. Hence, people may have suffered less jet lag on the return flight than might be expected, making it harder to detect effects. In the second RCT, the data suggested that melatonin may have reduced jet lag after 3 days, but the RCT did not test this.

One RCT reported details of the source of melatonin; most did not state the pharmaceutical form used. [2] Some melatonin products have been found to contain unidentified impurities. [1] The review concluded that "the pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established". [2]

OPTION HYPNOTICS (BENZODIAZEPINES; ZOPICLONE; ZOLPIDEM; ZALEPLON)

- For GRADE evaluation of interventions for Jet lag, see table, p 16 .
- Hypnotics (zopiclone or zolpidem), taken before bedtime on the first few nights after flying, may reduce the effects of jet lag by improving sleep quality and duration but not other components of jet lag.
- Hypnotics are associated with adverse effects including headache, dizziness, nausea, confusion, and amnesia. Short-term benefits of hypnotics must be considered in the light of potential adverse effects.

Benefits and harms

Hypnotics versus placebo:

We found no systematic review but found three RCTs. [3] [4] [5]

Severity of jet lag

Hypnotics compared with placebo The effect of hypnotics (zopiclone and zolpidem) on severity of jet lag are unclear (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of jet lag					
[3] RCT	33 people, westward flight crossing 5 time zones	**Subjective jet lag scores (see Comment) , first, second, fifth, and sixth days after the flight** with zopiclone (taken 30 minutes before bedtime on the first 4 nights after the flight) with placebo Absolute results not reported	Not significant	⟷	Not significant
[5] RCT **4-armed trial**	137 people, eastward flight crossing 5–9 time zones	**Alleviating symptoms of jet lag (see Comment) , fourth day after the flight** with zolpidem alone taken during the flight and at bedtime for 4 consecutive days after the flight with placebo Absolute results not reported The remaining arms evaluated melatonin alone and zolpidem plus melatonin	P <0.05	○○○	zolpidem alone

No data from the following reference on this outcome. [4]

Sleep quality

Hypnotics compared with placebo Hypnotics (zopiclone and zolpidem) seem to be more effective than placebo at improving sleep duration and quality (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[3] RCT	33 people, westward flight crossing 5 time zones	**Sleep duration , 2 nights after the flight** with zopiclone (taken 30 minutes before bedtime on the first 4 nights after the flight) with placebo Absolute results not reported	P <0.05	○○○	zopiclone
[3] RCT	33 people, westward flight crossing 5 time zones	**Sleep duration , 3 nights after the flight** with zopiclone (taken 30 minutes before bedtime on the first 4 nights after the flight) with placebo Absolute results not reported	P <0.01	○○○	zopiclone
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Mean number of awakenings , the first 2 nights after the flight** with zolpidem (taken immediately before bedtime on the first 3 nights after the flight) with placebo Absolute results not reported	P <0.05	○○○	zolpidem
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Sleep quality (measured using a 4-point rating scale) , the first 3 nights after the flight** with zolpidem (taken immediately before bedtime on the first 3 nights after the flight) with placebo Absolute results not reported	P <0.05	○○○	zolpidem
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Overall self-rated sleep quality (measured using a 5-point rating scale) , during the flight** with zolpidem alone taken during the flight and at bedtime for 4 consecutive days after the flight with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin	P <0.05	○○○	zolpidem alone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Headache** 12/68 (18%) with zolpidem 6/65 (9%) with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Rhinitis** 2/68 (3%) with zolpidem 1/65 (2%) with placebo			
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Diarrhoea** 2/68 (3%) with zolpidem 1/65 (2%) with placebo			
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Abnormal dreaming** 2/68 (3%) with zolpidem 0/65 (0%) with placebo			
[4] RCT	133 people aged 25–65 years who had travelled overseas at least twice during the past 24 months, eastward flights crossing 5–9 time zones	**Sinusitis** 0/68 (0%) with zolpidem 2/65 (3%) with placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Number of people with adverse effects** 6/34 (18%) with zolpidem 3/39 (8%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Nausea** 4/34 (12%) with zolpidem 1/39 (3%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Vomiting** 2/34 (6%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Confusion** 2/34 (6%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Dizziness** 1/34 (3%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Headache** 1/34 (3%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Palpitations** 1/34 (3%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Sweating** 0/34 (0%) with zolpidem 1/39 (3%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Dry mouth** 1/34 (3%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Incapacitation** 0/34 (0%) with zolpidem 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem plus melatonin			

No data from the following reference on this outcome. [3]

Zolpidem plus melatonin versus placebo:

We found no systematic review but found one RCT. [5]

Severity of jet lag

Zolpidem plus melatonin compared with placebo Zolpidem plus melatonin may be no more effective than placebo at reducing the symptoms of jet lag (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of jet lag					
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Alleviating symptoms of jet lag (see Comment) , fourth day after the flight** with zolpidem plus melatonin during the flight and at bedtime for 4 consecutive days after the flight with placebo Absolute results not reported The remaining arms evaluated melatonin alone and zolpidem alone	Reported as not significant	⟷	Not significant

Sleep quality

Zolpidem plus melatonin compared with placebo Zolpidem plus melatonin may be more effective than placebo at improving sleep quality during an eastward flight crossing 6–9 time zones (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Overall self-rated sleep quality (measured using a 5-point rating scale) , during the flight** with zolpidem plus melatonin during the flight and at bedtime for 4 consecutive days after the flight with placebo Absolute results not reported The remaining arms evaluated melatonin alone and zolpidem alone	P <0.05	○○○	zolpidem plus melatonin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Number of people with adverse effects** 7/29 (24%) with zolpidem plus melatonin 3/39 (8%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Nausea** 4/29 (14%) with zolpidem plus melatonin 1/39 (3%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Vomiting** 2/29 (7%) with zolpidem plus melatonin 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Confusion** 4/29 (14%) with zolpidem plus melatonin 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Dizziness** 2/29 (7%) with zolpidem plus melatonin 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Headache** 2/29 (7%) with zolpidem plus melatonin 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Palpitations** 0/29 (0%) with zolpidem plus melatonin 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Sweating** 1/29 (3%) with zolpidem plus melatonin 1/39 (3%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Dry mouth** 1/29 (3%) with zolpidem plus melatonin 0/39 (0%) with placebo The remaining arms evaluated melatonin alone and zolpidem alone			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Incapacitation** 1/29 (3%) with zolpidem plus melatonin 0/39 (0%) with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated melatonin alone and zolpidem alone			

No data from the following reference on this outcome. [3]

Zolpidem plus melatonin versus zolpidem alone:
We found no systematic review but found one RCT. [5]

Severity of jet lag

No data from the following reference on this outcome. [5]

Sleep quality

Zolpidem alone compared with zolpidem plus melatonin We don't know whether zolpidem alone and zolpidem plus melatonin differ in effectiveness at improving sleep quality and duration (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Overall self-rated sleep quality (measured using a 5-point rating scale) , during the flight** with zolpidem plus melatonin during the flight and at bedtime for 4 consecutive days after the flight with zolpidem alone during the flight and at bedtime for 4 consecutive days after the flight Absolute results not reported The remaining arms evaluated melatonin alone and placebo	Reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Number of people with adverse effects** 7/29 (24%) with zolpidem plus melatonin 6/34 (18%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT	137 people, eastward flight crossing 6–9 time zones	**Nausea**			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial		4/29 (14%) with zolpidem plus melatonin 4/34 (12%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Vomiting** 2/29 (7%) with zolpidem plus melatonin 2/34 (6%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Confusion** 4/29 (14%) with zolpidem plus melatonin 2/34 (6%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Dizziness** 2/29 (7%) with zolpidem plus melatonin 1/34 (3%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Headache** 2/29 (7%) with zolpidem plus melatonin 1/34 (3%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Palpitations** 0/29 (0%) with zolpidem plus melatonin 1/34 (3%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Sweating** 1/29 (3%) with zolpidem plus melatonin 0/34 (0%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Dry mouth** 1/29 (3%) with zolpidem plus melatonin 1/34 (3%) with zolpidem alone The remaining arms evaluated melatonin alone and placebo			
[5] RCT **4-armed trial**	137 people, eastward flight crossing 6–9 time zones	**Incapacitation** 1/29 (3%) with zolpidem plus melatonin 0/34 (0%) with zolpidem alone			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated melatonin alone and placebo			

Further information on studies

[3] The RCT assessed subjective jet lag scores using a 100 mm visual analogue scale; jet lag symptoms were described as: feeling tired at unusual times of the day, bad mood, feeling of ill-being, digestive problems, and absence of energy.

[5] The RCT used a 100 mm visual analogue scale to assess the severity of jet lag symptoms and effectiveness of medication.

Comment: **Clinical guide:**
Disruption of sleep is a major component of jet lag, and hypnotics have been used to try to reduce it. The short-term benefit seems to be outweighed by the wide range of unpleasant effects, some of them common.

OPTION LIFESTYLE AND ENVIRONMENTAL ADAPTATIONS (EATING, AVOIDING ALCOHOL OR CAFFEINE, SLEEPING, DAYLIGHT EXPOSURE, AROUSAL)

- For GRADE evaluation of interventions for Jet lag, see table, p 16 .
- We don't know whether lifestyle or environmental adaptations (such as eating, avoiding alcohol or caffeine, sleeping, daylight exposure, or arousal) are effective as we found insufficient high-quality evidence.
- After a westward flight, it is worth staying awake while it is daylight at the destination and trying to sleep when it gets dark. After an eastward flight, one should stay awake but avoid bright light in the morning, and be outdoors as much as possible in the afternoon. This will help to adjust the body clock and turn on the body's own melatonin secretion at the right time.

Benefits and harms

Lifestyle adaptations (eating, avoiding alcohol or caffeine, sleeping, daylight exposure, or arousal) versus no lifestyle adaptations:

We found no systematic review or RCTs looking at the lifestyle and environmental adaptations of eating, avoiding alcohol or caffeine, sleeping, daylight exposure, or arousal (i.e., doing interesting things such as sightseeing or visiting friends; see Comment).

Different types of artificial light exposure versus each other:

We found one RCT (20 people aged 21–34 years) comparing artificial bright white light via a head-mounted light visor with artificial dim red light for 3 hours on the first two evenings after a westward flight crossing six time zones. [6]

Severity of jet lag

Artificial bright white light compared with artificial dim red light We don't know whether artificial bright white light for 3 hours each evening is more effective than artificial dim red light at reducing the severity of jet lag after 2 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of jet lag					
[6] RCT	20 people aged 21–34 years, westward flight crossing 6 time zones	**Jet lag (rated subjectively) , 2 days** with artificial bright white light via a head-mounted light visor on the first 2 evenings with artificial dim red light for 3 hours on the first 2 evenings Absolute results not reported	Reported as not significant	⟷	Not significant
[6] RCT	20 people aged 21–34 years, westward flight crossing 6 time zones	**Salivary melatonin (to detect the onset of evening secretion) , 2 days** with artificial bright white light via a head-mounted light visor on the first 2 evenings with artificial dim red light for 3 hours on the first 2 evenings Absolute results not reported Bright light produced a mean delay in salivary melatonin secretion of 1 hour compared with dim light (i.e., put the body clock 1 hour forward)			

Sleep quality

Artificial bright white light compared with artificial dim red light We don't know whether artificial bright white light for 3 hours each evening is more effective than artificial dim red light at improving sleep quality after 2 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[6] RCT	20 people aged 21–34 years, westward flight crossing 6 time zones	**Sleep quality (rated subjectively) , 2 days** with artificial bright white light via a head-mounted light visor on the first 2 evenings with artificial dim red light for 3 hours on the first 2 evenings Absolute results not reported	Reported as not significant	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [6]

Comment: RCTs on the effects of lifestyle and environmental adaptation are unlikely to be performed.

Clinical guide:
Much physiological and anecdotal evidence supports environmental adaptation. Light is the major external environmental cue that pushes the circadian phase towards the light–dark rhythm at the

destination. Endogenous melatonin production by the pineal gland is switched on by darkness, normally at dusk, and is inhibited by bright light. [2] After a westward flight, it is probably worth staying awake while it is daylight at the destination and trying to sleep when it gets dark; and, after an eastward flight, being awake but avoiding bright light in the morning, and being outdoors as much as possible in the afternoon. [1] [7] Such behaviour may adjust the body clock and turn on the body's own melatonin secretion at the right time. Other cues may reinforce the effect of light, such as eating modestly at the times that correspond to usual meal times, and taking comfortable exercise. [1]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Melatonin: one systematic review updated. [2] Categorisation unchanged (likely to be beneficial).

REFERENCES

1. Herxheimer A, Waterhouse J. The prevention and treatment of jet lag. *BMJ* 2003;326:296–297.[PubMed]
2. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. In: The Cochrane Library, Issue 12, 2013. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.[PubMed]
3. Daurat A, Benoit O, Buguet A. Effects of zopiclone on the rest/activity rhythm after a westward flight across five time zones. *Psychopharmacology* 2000;149:241–245.[PubMed]
4. Jamieson AO, Zammit GK, Rosenberg RS, et al. Zolpidem reduces the sleep disturbance of jet lag. *Sleep Med* 2001;2:423–430.[PubMed]
5. Suhner A, Schlagenhauf P, Hofer I, et al. Effectiveness and tolerability of melatonin and zolpidem for the alleviation of jet lag. *Aviat Space Environ Med* 2001;72:638–646.[PubMed]
6. Boulos Z, Macchi MM, Sturchler MP, et al. Light visor treatment for jet lag after westward travel across six time zones. *Aviat Space Environ Med* 2002;73:953–963.[PubMed]
7. Waterhouse JM, Minors DS, Waterhouse ME, et al. Keeping in time with your body clock. Oxford, UK: Oxford University Press, 2002.

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GRADE **Evaluation of interventions for Jet lag.**

Important outcomes			Severity of jet lag, Sleep quality						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to prevent or minimise jet lag?									
At least 6 (at least 232) [2]	Severity of jet lag	Melatonin versus placebo	4	0	0	–2	0	Low	Directness points deducted for non-standardised formulation of melatonin and different regimens
1 (234) [2]	Sleep quality	Melatonin versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for unclear outcome definition
2 (170) [3] [5]	Severity of jet lag	Hypnotics versus placebo	4	–2	–1	0	0	Very low	Quality point deducted for sparse data and incomplete reporting of results; consistency point deducted for conflicting results
3 (303) [3] [4] [5]	Sleep quality	Hypnotics versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (137) [5]	Severity of jet lag	Zolpidem plus melatonin versus placebo	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
1 (137) [5]	Sleep quality	Zolpidem plus melatonin versus placebo	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
1 (137) [5]	Sleep quality	Zolpidem plus melatonin versus zolpidem alone	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
1 (20) [6]	Severity of jet lag	Different types of artificial light exposure versus each other	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
1 (20) [6]	Sleep quality	Different types of artificial light exposure versus each other	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.